

# Avian Influenza: Potential Impact on Sub-Saharan Military Populations with High Rates of Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome

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Several sub-Saharan militaries have large percentages of troops with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome. With the arrival of avian influenza in Africa, the potential exists that some of those soldiers might also become infected with H5N1, the virus responsible for the disease. Two possible scenarios have been postulated regarding how such a coinfection of HIV and H5N1 might present. (1) Soldiers already weakened by HIV/acquired immunodeficiency syndrome rapidly succumb to H5N1. The cause of death is a "cytokine storm," essentially a runaway inflammatory response. (2) The weakened immune system prevents the cytokine storm from occurring; however, H5N1 is still present, replicating, and being shed, leading to the infection of others. A cytokine storm is particularly dangerous for individuals of military age, as evidenced by the large number of soldiers who died during the 1918 influenza epidemic. If large numbers of sub-Saharan soldiers suffer a similar fate from avian influenza, then military and political instability could develop.

## Introduction

Avian influenza, also known as bird flu, is caused by viruses that normally infect only birds and, less frequently, pigs.<sup>1</sup> Although the viruses are highly species specific, they have on rare occasions crossed the species barrier to infect humans. Such is the case with avian influenza A (H5N1), the present cause of much concern. The World Health Organization (WHO) reports that human infections caused by direct transmission of avian influenza viruses from birds, H5N1, is responsible for the largest number of cases of severe disease or death.<sup>2</sup> A devastating pandemic could ensue if the virus eventually acquires the ability to be easily transmitted among humans.<sup>3</sup>

This increased transmissibility might occur through an antigenic shift, where two different influenza strains genetically recombine to form a new subtype. In the past, this mechanism, involving viruses other than H5N1, has been responsible for several major influenza outbreaks, including the Asian (H2N2) and Hong Kong (H3N2) influenza pandemics of 1955 and 1968, respectively.<sup>4</sup>

The relatively recent arrival of H5N1 in Africa, where human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) is endemic in many countries, raises both concerns and uncertainties, including those of a military nature. Currently, it is not known what the outcome would be if people

with HIV/AIDS became coinfecting with H5N1. Because many sub-Saharan African militaries have large percentages of soldiers with HIV/AIDS, especially in comparison with their corresponding civilian populations, questions exist regarding what effect avian influenza might have on such troops, as well as their comrades, and whether it could affect military capabilities.<sup>5</sup>

If large numbers of sub-Saharan troops are killed or incapacitated by the avian flu, then it is possible that some countries would suffer internal instability. Other countries might take advantage of such situations, with the result that regional conflicts could erupt. Besides the enormous human toll that could result from the fighting, important exports to the United States, including oil, could be significantly disrupted.

With several peacekeeping missions involving African troops, there is an additional concern that they could be responsible for disseminating H5N1 to other regions. Their close contact with civilian populations in host countries, and the potentially large number of subsequent fatalities from the disease, could cause instability in countries originally spared from avian influenza.

By examining medical, military, and political scenarios that might occur if large numbers of African troops become coinfecting with HIV/AIDS and H5N1, it is hoped that measures can be developed to mitigate or even prevent the worst possible outcomes. In an era of increasing globalization, providing effective interventions would probably benefit not only the countries of Africa but also other nations, including the United States.

## Geographic Spread of the Disease

H5N1 has been significantly more widespread in poultry and wild birds than in people. The virus possibly arose in birds in southern China before 1997.<sup>6</sup> By mid-2003, large numbers of birds in Asia were infected, although this initially went undetected and unreported. The disease continued to spread among birds, and it is now considered endemic in many parts of Vietnam and Indonesia, as well as some areas of Cambodia, China, Thailand, and possibly the Lao People's Democratic Republic. Other countries in Asia and Europe have also reported infected poultry and/or wild birds, although not to the extent that the disease would be considered endemic. Three countries, namely, Japan, the Republic of Korea, and Malaysia, had outbreaks of H5N1 in poultry but were able to control them, at least initially, through methods such as destroying the birds. Indeed, killing infected poultry is considered one of the cornerstones in the strategy to combat avian influenza. Because the disease appears to be transmitted to people via prolonged contact with H5N1-positive birds, methods such as destroying these animals possibly help to prevent the spread of disease to other flocks as well as to humans. It should be noted that, although birds at least

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are a large reservoir of the virus and likely are a direct vector for human infection, animals such as dogs and cats, which feed on infected birds, are being considered as possible intermediate mammalian vectors, which is why South Korea, in attempting to control an outbreak of H5N1, plans to cull them.<sup>7</sup>

In Africa, the virus was first detected on a Nigerian farm on February 8, 2006.<sup>8</sup> It is unclear whether the poultry had been infected by migrating birds or chickens smuggled from abroad. To some extent the location was a surprise, because many experts thought that the continent's initial outbreak would occur further east, where migratory birds from Europe and Asia stop to rest before continuing their journey.<sup>9</sup>

The first outbreak of H5N1 among humans was reported in Hong Kong in 1997.<sup>10</sup> Of the 18 people infected, 6 died. The disease struck humans again in 2003, this time in a family that had recently traveled to Fujian Province, China. Eventually, the disease began to occur in people beyond the Chinese borders; near the end of 2006, 10 countries had reported laboratory-confirmed cases of H5N1 in humans.

### Potential for Pandemic

To date, H5N1 appears to have been transmitted to people mainly through exposure (usually of a prolonged nature) to infected birds. This limited means of transmission has resulted in a relatively small number of reported avian flu cases in humans, i.e., 258 as of mid-November 2006, although 153 of those people died.<sup>11</sup> However, if the virus improved its ability to infect humans and acquired human-to-human transmission capability, then a pandemic could ensue; if it maintained its virulence, then the result would be catastrophic. Such was the case in 1918, when an influenza virus mutated and, unwittingly transported and transmitted by troops engaged in World War I, resulted in the deaths of tens of millions of people worldwide. In this era of jet transportation, it could be expected that a disease transmitted via human-to-human transmission would be disseminated significantly more quickly than the flu was in 1918.

It is important to realize that, when discussing the possibility of a mutation leading to efficient human-to-human transmission and causing a pandemic, we are generally referring to the spread of the disease via aerosol, whereby individuals who are uninfected inhale respiratory droplets from those who are infected. Once again, this is what occurred in 1918.

H5N1 might develop, or possibly already possess, the ability to be transmitted via the fecal-to-oral route.<sup>12</sup> An outbreak of this type could resemble and possibly be confused with other diseases spread this way, such as cholera. This is a less efficient human-to-human mode of spreading disease, compared with the airborne respiratory route, but could still lead to clusters of individuals with avian influenza. In countries lacking the capability to monitor disease outbreaks, these clusters might grow quite large. However, in countries with better developed public health systems, measures could be implemented to contain a disease spread via this method, thus averting a pandemic. Therefore, although the relatively inefficient fecal-to-oral-type spread could lead to very damaging regional outbreaks, the virus would likely need to be spread by the efficient airborne respiratory route to pose an international pandemic threat.

Global surveillance has been established in an attempt to track the geographic dispersion of avian influenza in both birds

and humans. From its possible origin in Asia, the disease has spread to Europe and most recently Africa. It is hoped that, when the disease is detected in a new area, its further spread can be prevented or at least impeded through public health measures such as destruction of infected birds.

The fear now is that Africa, which is often described in the literature as the weak link in the global surveillance network, could experience a significant outbreak of the disease not only among poultry, upon which so many people depend for their protein, but also among humans who have prolonged contact with such animals. Poor medical and scientific infrastructures, including a dearth of physicians and scientists, plague a large number of the countries on the continent. Therefore, many African governments are unable to marshal the resources required to effectively monitor for avian influenza.<sup>13</sup> If the disease were to become established on the continent, then many of the countries would probably also have only a limited ability to deal effectively with the medical needs of large numbers of people sick with the disease. Indeed, many African nations are already straining to deal with malaria, malnutrition, and HIV/AIDS among their populations.

WHO-led teams have been instrumental in serving as resources for countries battling, or preparing to battle, H5N1. In Nigeria, the teams searched patient records at hospitals in the vicinity of the farm where H5N1 was first detected in poultry.<sup>14</sup> Blood samples were collected from four patients and sent to the United Kingdom for testing at a WHO-collaborating laboratory. However, this was only one relatively small area in a vast continent. Even with WHO assistance, a continent-wide outbreak would quickly overwhelm the medical resources of most, if not all, of the African nations.

### Increased Lethality of Avian Influenza among Militaries

Examining the 1918 flu pandemic, which has been postulated as having arisen either near or at Fort Riley, Kansas, one can readily see how military living could be conducive to the spread of influenza. John Barry's excellent book, *The Great Influenza*, details some of those conditions, many of which exist today among certain African militaries.<sup>15</sup> These conditions include close living quarters, troop movements among in-country bases as well as to other nations, inadequate medical resources, and a lack of preparation for disease outbreaks.

The parallels between the 1918 U.S. military and many of the armies in present day Africa are not reassuring. Whereas the United States has instituted numerous public health measures in the military since the pandemic to help mitigate the spread of disease, many African militaries are unable to make all of the necessary improvements. For example, the U.S. military, in preparing for a possible avian influenza outbreak, has stockpiled antiviral medications.<sup>16</sup> Additionally, the military has developed plans, such as isolation or quarantine of soldiers, to contain an outbreak.<sup>17</sup> Such stockpiles and extensive planning may not be universally possible among sub-Saharan nations that are impoverished. If avian influenza breaks out among their soldiers, the ability of those militaries to limit its spread not only to other soldiers but also to the civilian population is doubtful.

The question may be asked, "Why should avian influenza be of particular concern to militaries?" After all, influenza is often

most dangerous to the very young and very old, whereas troops are generally neither. This is true for many of the influenza strains but not for the one that caused the 1918 pandemic and probably not for H5N1. Because both of these strains seem to incite a strong immune response, young people (such as those of military age), who have a strong immune system, mount such a strong response that they have a cytokine storm. Ironically, it is because soldiers are generally young and healthy that they are likely to have serious complications when infected with certain strains of influenza.

### Scenarios of Coinfections of HIV/AIDS and H5N1

H5N1, the etiological agent of the avian influenza, appears to kill through what has become known as a cytokine storm, although this metaphor is not without its detractors.<sup>18</sup> Cytokines, small regulatory proteins, are how cells signal other cells, in much the way that hormones are how organs signal other organs. Unfortunately, in avian influenza, the cytokines responsible for promoting inflammation are not counterbalanced, through a negative feedback mechanism, by other cytokines trying to calm the reaction down. The body essentially develops an overwhelming inflammatory response that, in the process of trying to kill the virus, sometimes manages to kill the host.

Because death is attributable to an overreactive immune response, two unique and essentially opposite outcomes have been postulated if people with HIV/AIDS become coinfectd with avian influenza.<sup>19</sup> These possibilities can be examined with regard to sub-Saharan militaries. The possibilities are (1) a significant percentage of soldiers with HIV/AIDS succumbing rapidly to either avian flu or secondary infections because of their weakened immune systems or (2) a significant percentage of soldiers with HIV/AIDS who acquire the avian flu virus remaining relatively asymptomatic but serving as a reservoir for the disease. Avian flu often kills its host by inducing a massive inflammatory response (cytokine storm), and a person with a compromised immune system might not mount a vigorous response to the virus. Such a person could, theoretically, continue to shed the virus. Because soldiers often live in close quarters with other soldiers, if H5N1 acquired the ability to be transmitted from human to human, then it is likely that other soldiers would also develop the avian flu.

This second scenario presents an unusual twist, in that the normal self-limiting nature of markedly virulent microbes, where death of the host can help limit the spread of the disease, is absent. As a result, such persons would serve as reservoirs for the avian flu.

It is possible that both scenarios are feasible, with the actual outcome depending on the individual's CD4<sup>+</sup> cell count. If the count is relatively normal, then the HIV-positive person might sustain a response similar to that of an individual who is not HIV positive (that is, a cytokine storm, with the risk of death from an overwhelming inflammatory response). If the CD4<sup>+</sup> cell count is a bit low, then a large immune reaction might not occur but, because the person is already weak (possibly from other infections), he or she might still die. Lastly, if the CD4<sup>+</sup> cell count is quite low, then perhaps there might be no significant immune response and no outward signs, at least initially, of an avian influenza infection. This person would succumb to AIDS but possibly not before spreading H5N1.

Currently, it is uncertain which, if any, of the scenarios would occur. Additionally, the outcomes might be dependent on several factors, of which CD4<sup>+</sup> cell count is only one. These might include vaccination history, the presence of comorbidities, available medical care, and other factors not readily discernible at this time.

### Possible Increased Likelihood of Antigenic Shift

If a person with HIV/AIDS does not fatally succumb to avian influenza but instead harbors it in his or her system, then the possibility exists that this increased time in a host could be conducive to a dangerous antigenic shift of the H5N1 virus. This might occur if the person is infected not only with HIV and H5N1 but also with another flu strain, one that is not particularly virulent but is readily transmissible between people. With H5N1 coexisting with this less virulent strain, genes could be transferred between the two, with the unfortunate result that H5N1 acquires genetic material responsible for human-to-human transmissibility. If H5N1 retains its virulence and gains human-to-human transmissibility from the other flu virus, then a pandemic could ensue.

The question of whether such a recombined H5N1 would retain its virulence is a significant one, however; based on the historical record, the answer seems to be no. The origin of the virus from the 1918 pandemic, which was exceptionally virulent, is still uncertain, although it does not seem that it was widely circulating in humans immediately before the outbreak and it does not appear to have made the cross-species jump directly from birds to people.<sup>20</sup> A reasonable but uncertain assumption based on the available evidence is that the virus was created through small mutations of an existing virus.<sup>21</sup>

This situation contrasts with isolates from pandemics in which the virulence was relatively mild. There the infectious agent often appears to be the result of two viruses sharing their information. Therefore, if the norm is generally for recombination to produce a milder virus, then it is quite possible that coinfection with H5N1 and another influenza virus may lead to a milder form of avian flu, even if it adopts human-to-human transmissibility. This is speculative, of course, and it is uncertain what virulence a recombinant might actually have. With a large pool of individuals coinfectd with both viruses, it is possible several variants could emerge, some more virulent than others.

### Sub-Saharan Militaries and HIV/AIDS

Before the outbreak of H5N1 in Nigerian poultry, experts predicted that the region most likely to be hardest hit would be around the lakes of the Rift Valley.<sup>22</sup> There, large numbers of migratory birds from Europe and Asia stop to refresh themselves. It is an area still vulnerable to avian influenza, either from progression eastward from Nigeria or from the resting migratory birds.

Sub-Saharan militaries draw some of their soldiers from countries where there have already been confirmed outbreaks or there are risks of outbreaks of avian influenza.<sup>23</sup> It is therefore possible that a young recruit (perhaps a poultry farmer) infected with H5N1 but still asymptomatic could find his way to a large, crowded, military camp. This is possibly how influenza erupted at U.S. military bases in 1918.



When considering the possible impact of avian influenza on soldiers with HIV, it is worthwhile to look at the prevalence rates of HIV in African militaries. Unfortunately, not all African countries have accurate data regarding their troops and HIV. As an example, Zimbabwe has an HIV prevalence rate of 33.7% in the general population.<sup>24</sup> However, because it has not tested the military as a subset, the rate among the troops is unknown (although it is suspected to be even higher than in the general population).

Even when countries do report their HIV prevalence rates, uncertainty exists with respect to their accuracy, in part because of questions regarding the extent of reliable testing.<sup>25</sup> Keeping this in mind, the reported HIV prevalence rates for some of the African militaries in countries where there have been confirmed cases of avian influenza in birds, as well as those near the originally predicted epicenter of an east African outbreak, are as follows: Nigeria, 8%; Cameroon, 9.8%; Kenya, 7%; Tanzania, 23%; Uganda, 8%; Ethiopia, 7%.<sup>26-31</sup> With extended separation from their families and possibly increased contact with commercial sex workers, many units deployed on peacekeeping missions have even higher HIV prevalence rates than the overall military.<sup>32</sup>

Several of these African militaries, as members of the African Union (AU), are involved or possibly will be involved in foreign peacekeeping operations. There is a Kenyan contingent with the AU that is currently deployed to Darfur (part of the Sudan), attempting to restore order to that troubled region.<sup>33</sup> Elsewhere, Uganda, Ethiopia, and Kenya were to send troops to help secure Somalia for the reestablishment of a government, although the deployment ran into difficulties.<sup>34</sup> If avian influenza occurs among deploying African troops after the virus has gained human-to-human transmissibility, then the likelihood of the disease spreading to areas away from the initial cases is greatly increased. If some of the peacekeepers who have H5N1 are coinfecting with HIV and have an increased period in which they can transmit H5N1, compared with troops who are not HIV positive, then the chance of spreading the disease increases even more.

Such a scenario, that is, peacekeepers with HIV spreading disease, appears to have occurred, with the disease being HIV itself.<sup>35</sup> Then-U.S. Ambassador to the United Nations Richard Holbrooke, in a statement to the U.N. Security Council in January 2001, and not referring just to Africa, stated, "I regret to say that AIDS is being spread, among other people, by peacekeepers."<sup>36</sup> It would not be surprising if avian influenza eventually followed a similar pattern.

### Possible Instability

If large numbers of African soldiers die, then internal instability could ensue, especially in countries that are dependent upon soldiers to also serve as the police force. Additionally, neighboring countries could be tempted to take advantage of such instability. Africa seems to have an almost unlimited supply of potential flashpoints, and the chance to settle old border grievances might be tempting to one country while its neighbor suffers internal turmoil.

Additional problems could potentially arise because of the previously mentioned role of AU troops in peacekeeping. Besides the AU not being able to raise troops because of so many soldiers

in its member states being sick, other countries may be hesitant to host peacekeepers from areas where avian influenza has occurred.

### Possible Interventions

To decrease the likelihood of African soldiers dying from avian influenza, public health measures should be implemented, such as monitoring for the disease and preparing to institute quarantines. Because many African nations lack adequate resources for such undertakings, wealthier nations might consider assisting them.

An additional measure to consider, one that would be directed toward soldiers who are positive for HIV/AIDS, is the provision of antiretroviral drugs. If maintaining an elevated CD4<sup>+</sup> cell count would help prevent the creation of a H5N1 strain with human-to-human transmissibility, then this would be an additional incentive to increase the use of antiretroviral therapies among African militaries that have high percentages of soldiers with AIDS. Once again, because some countries are unable to meet the need on their own, assistance from Western governments might be necessary. Model programs already exist.<sup>37</sup> With 23% of its 75,000 troops infected with HIV, the South African military has been hit particularly hard by AIDS. In 2002, 7 of every 10 deaths among South African troops were AIDS-related. A 5-year collaboration between members of the U.S. National Institute of Allergy and Infectious Diseases and the South African military was initiated in 2003, for the dual purpose of testing for HIV and providing some antiretroviral drugs for the armed forces. Additional projects implemented by the United States have provided several African militaries with resources to assist in HIV prevention.

### Conclusions

Bird flu made its first confirmed African appearance in Nigeria on February 8, 2006. By the middle of March, it was in three other countries on the continent.<sup>38</sup> With a strong tradition in many rural African communities of people having close contact with wild and/or domestic birds, it is quite possible that an African villager will become infected with H5N1 and then report to military duty before the disease manifests itself.

The question exists regarding what would happen to that soldier, who already has H5N1, if he also has HIV/AIDS. Two scenarios have been postulated. In the first, already weakened by HIV/AIDS, the soldier quickly succumbs to the cytokine storm caused by avian influenza. In the second, HIV/AIDS prevents the cytokine storm from occurring, and the soldier continues to shed H5N1 without exhibiting significant signs and/or symptoms of illness. If H5N1 acquires the ability to be transmitted from human to human, then this second scenario could lead to avian influenza being silently and rapidly disseminated. With many sub-Saharan African nations having a high percentage of their military populations with HIV/AIDS, either scenario could potentially lead to the incapacitation or death of significant numbers of soldiers. These reductions in the armed forces could result in military and/or political instability.

It is important to remember that, at this time, much of what we think could happen among African soldiers with HIV/AIDS who develop a coinfection with H5N1 is speculative. Besides

being ethically wrong, discrimination against such soldiers (such as threatening to discharge them from the service) could prove to be counterproductive. In many African militaries the HIV test is voluntary, with the result that numerous soldiers already decline to take it, in part because they fear the stigma associated with being HIV-positive. Adding more burdens would only further discourage them from finding out their HIV status.

A better approach, we think, would be to work with soldiers who are in various stages of HIV/AIDS. A collaborative noncoercive approach could go far to answering numerous questions. What happens when people with HIV become coinfectd with H5N1? Does the CD4<sup>+</sup> cell count influence the outcome? Can providing antiretroviral drugs lead to a potentially lethal cytokine storm? Further research is needed to answer these and other questions.

Strengthening the public health capabilities in poor regions of Africa, especially as they relate to detecting H5N1 and implementing appropriate measures to prevent its spread, is a critical and often difficult requirement. Nations that do not have the financial and/or technical capabilities to meet this challenge will require money and/or expertise from wealthier countries.

An avian influenza pandemic could cost tens of millions of lives. To help avert this catastrophe, it is important that the United States consider offering assistance to help African nations that have high percentages of soldiers with HIV/AIDS prevent these troops from becoming coinfectd with H5N1. For troops that do become coinfectd, the endeavor should be both to save their lives and to prevent further dissemination of the disease. These efforts are not just for humanitarian reasons, but they are also in our own best interests.

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